INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000242

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J3/00 C07J31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/24365 A (GLAXO GROUP LTD ;BIGGADIKE KEITH (GB); PROCOPIOU PANAYIOTIS ALEXAN) 10 July 1997 (1997-07-10) page 11, line 25 - page 13, line 6	1-22
X	WO 02/08243 A (COOTE STEVEN JOHN ;ROBINSON JOHN MALCOLM (GB); GLAXO GROUP LTD (GB) 31 January 2002 (2002-01-31) page 6, lines 1-15	1-16
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X	US 4 578 221 A (BAIN BRIAN M ET AL) 25 March 1986 (1986-03-25) examples 1-13 claims 1,7	1-16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 August 2004	18/08/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Samsam Bakhtiary, M

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000242

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 02/12265 A (COOTE STEVEN JOHN ; BIGGADIKE KEITH (GB); GLAXO GROUP LTD (GB); NICE R) 14 February 2002 (2002-02-14) page 21, line 1 - page 22, line 25	1-16
X	HAPGOOD, JANET P. ET AL: "Steroid-affinity purification of the rat liver glucocorticoid hormone receptor complex" JOURNAL OF STEROID BIOCHEMISTRY (1987), 28(6), 769-77 CODEN: JSTBBK; ISSN: 0022-4731, 1987, XP001183044 page 770, right-hand column, paragraph 2	17,18
X	HOYTE, R. M. ET AL: "Synthesis and evaluation of potential radioligands for the progesterone receptor" JOURNAL OF MEDICINAL CHEMISTRY (1985), 28(11), 1695-9 CODEN: JMCMAR; ISSN: 0022-2623, 1985, XP001182782 page 1696, right-hand column; compound 15	17,18
X	MACINDOE, JOHN H. ET AL: "Comparative studies of 5.alpha.-reductase inhibitors within MCF-7 human breast cancer cells" JOURNAL OF STEROID BIOCHEMISTRY (1984), 20(5), 1095-100 CODEN: JSTBBK; ISSN: 0022-4731, 1984, XP001182781 page 1096, left-hand column, last paragraph - page 1096, right-hand column, line 11	17,18
X	FORMSTECHER, P. ET AL: "Synthesis of steroidal 17.beta.-carboxamide derivatives" STEROIDS (1980), 35(3), 265-72 CODEN: STEDAM; ISSN: 0039-128X, 1980, XP001182780 page 266 formula III	17-19
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Int[ ]nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	HEUBNER, ARNULF ET AL: "Application of liquid-liquid partition chromatography in the simultaneous purification of sex-hormone-binding globulin and corticosteroid-binding globulin" JOURNAL OF CHROMATOGRAPHY (1987), 397, 419-34 CODEN: JOCRAM; ISSN: 0021-9673, 1987, XP001194688 page 420, paragraph 4	17-19
X	PHILLIPPS G H ET AL: "SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS IN A SERIES OF ANTIINFLAMMATORY CORTICOSTEROID ANALOGUES, HALOMETHYL ANDROSTANE-17BETA-CARBOTHIOATES AND-17BETA-CARBOSELENOATES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 37, no. 22, 1 October 1994 (1994-10-01), pages 3717-3729, XP002025925 ISSN: 0022-2623 cited in the application page 3718 scheme 3	1-16
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PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
ALPHARMA APS
Dalslandsgade 11
DK-2300 Copenhagen S
DENMARK

Date of mailing (day/month/year): 18/08/2004

Applicant's or agent's file reference: 2003-100 PC

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.: PCT/DK2004/000242

International filing date (day/month/year): 02/04/2004

Applicant: ALPHARMA APS

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority:
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer: Josef Ullrich

CLAIMS

1. A method for preparing a steroidal carbothioic acid or a salt thereof, said method comprises:
A) reacting a steroidal carboxylic acid or a salt thereof with a coupling agent selected from the group consisting of carbodiimide derivatives represented by the following formula:

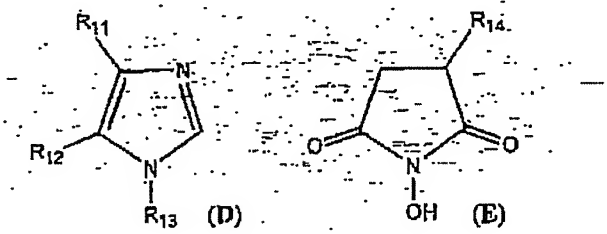
$R_a—N=C=N—R_b$

wherein R_a and R_b are the same or different, and each represent an aliphatic, heteroaliphatic, carbocyclic or a heterocyclic group [all said groups are optionally substituted];
alone or in conjunction with a coupling enhancer; and
B) reacting the product of step A) with a nucleophilic agent comprising a sulfur atom.

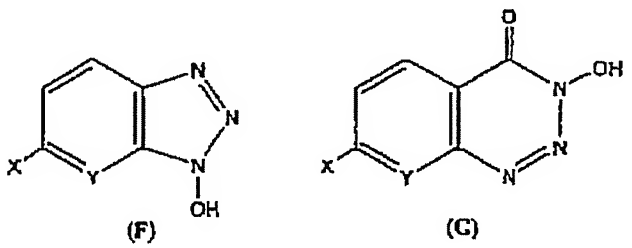
2. A method according to claim 1 in which the coupling agent is 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC).

3. A method according to claim 2, in which the coupling agent is the hydrochloride salt of EDC.

4. A method according to any of the preceding claims, in which the coupling enhancer is selected from the group consisting of:
A) a heterocyclic ring containing one or two nitrogen atoms, said ring being optionally substituted; such as a compound of formula (D) or formula (E),



wherein R_{11} and R_{12} can be the same or different, and each represent a hydrogen atom or a cyano group; R_{13} represent a hydrogen atom or an alkyl group; and R_{14} represent a hydrogen atom or a salt of a sulfonic acid such as sodium sulfonate [-S(=O)(=O)-O$^-$ Na^+]; and
B) an unsaturated 5-6 membered heterocyclic ring fused to an aromatic- or heteroaromatic ring in which the said heterocyclic ring contains three nitrogen atoms, said rings being optionally substituted, such as a compound of formula (F) or formula (G),



X = H, F, Cl, Br and Y = CH, N, O, S

AMENDED SHEET

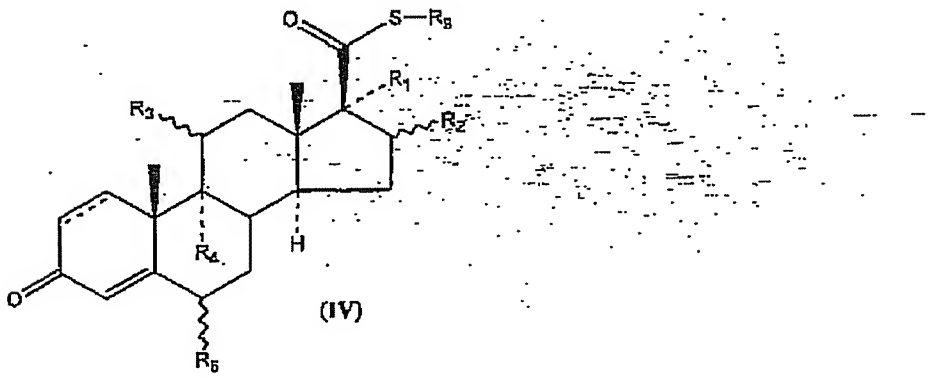
preferably 6-chloro-hydroxybenzotriasole (6-Cl-HOBt), 7-aza-hydroxybenzotriasole (HOAt), or 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (Dbht-OH).

5. A method according to any of the preceding claims, where the nucleophilic agent comprising a sulfur atom is selected from the group comprising:

- compounds of formula $[M]^+[SH]^-$ wherein M is a metal such as Li, Na or K; or $[M]^{2+}[S]^{2-}$ wherein M is a metal such as Ca or Mg, the said sulfide salts being optionally hydrated (such as sodium hydrosulfide hydrate); and
- an *in situ* generated sulfide salt or a hydrated sulfide salt.

6. The method of any of the preceding claims, wherein the nucleophilic agent is dissolved in a suitable solvent prior to addition to the reaction mixture, or wherein the nucleophilic agent is added in the form of a solid salt or as a solution of the salt in water and/or an organic solvent or a combination thereof.

7. A method according to any of the preceding claims for preparing a steroidal carbothioic acid of formula (IV) or a salt thereof



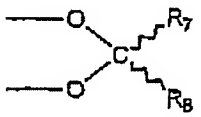
(IV)

Wherein the symbol ==== in the 1,2-position represent a single or a carbon-carbon double bond;

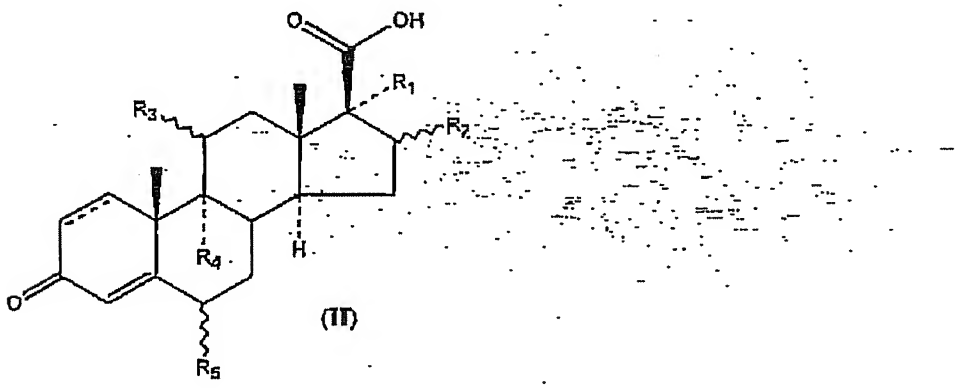
R_1 represents a hydrogen atom, a hydroxy- or an alkoxy group (such as an optionally substituted C_{1-6} alkoxy) in the α-configuration, a group -O-C(=O)-R_6, where R_6 is an alkyl group (such as optionally substituted C_{1-6} alkyl) or an optionally substituted 5-6 membered heterocyclic ring containing either oxygen, nitrogen or sulfur as ring hetero atom (such as a furanyl-, pyrrolyl- or a thiophenyl group);

R_2 represents a hydrogen atom, a hydroxy group, an alkoxy group (such as an optionally substituted C_{1-6} alkoxy) in the α-configuration, an alkyl group (such as an optionally substituted C_{1-6} alkyl) which may be in either the α- or β-configuration, an alkylene group (such as an optionally substituted C_{1-6} alkylene having the two free valencies on the same carbon atom,

preferably methylene) [the alkylene group bound to the steroid nucleus via a double bond] or R_1 and R_2 together represent



where R_7 and R_8 are the same or different and each represent a hydrogen atom or an alkyl group (such as an optionally substituted C_{1-6} alkyl);
R_3 represent a hydrogen atom, hydroxy- or a protected hydroxy group in either the α- or β-configuration or an oxo group (in which case the bond between R_3 and the steroid nucleus is a double bond);
R_6 represents a hydrogen- or a halogen atom or R_3 and R_4 together represent a carbon-carbon bond or an epoxy group in the β-configuration; and
R_5 represents a hydrogen- or a halogen atom in either the α- or β-configuration;
R_9 represents a hydrogen atom or R_9 represent a metal ion [eg. the molety $-S-R_9$ represents a group of the formula $[-S]^-[M]^+$ wherein M is a metal such as Li, Na or K]; the method comprising;
A) reacting a steroidal carboxylic acid of formula (II) or a salt thereof



(II)

in which the substituents of formula (II) have the above defined meaning with a coupling agent alone or in conjunction with an coupling enhancer, followed by the reaction with a nucleophilic agent comprising a sulfur atom; and optionally
B) reacting the product from step A) with an acid.

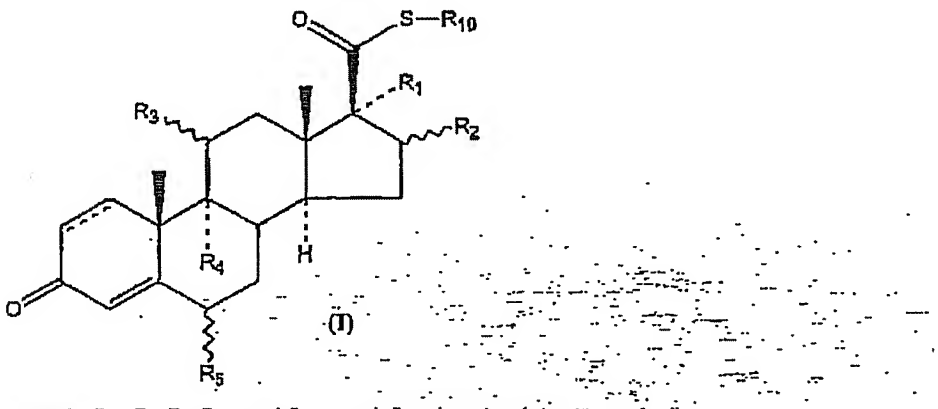
8. The method of any of the preceding claims, wherein I)
- the coupling agent is added before the coupling enhancer, or
- the coupling enhancer is added before the coupling agent, and/or wherein II)
- the steroidal carboxylic acid is added to a mixture of the coupling agent and the coupling enhancer, or wherein
- a mixture of the coupling agent and the coupling enhancer is added to a steroidal carboxylic acid, or wherein

- the steroidal carboxylic acid is added to a mixture of the coupling agent and the coupling enhancer in a polar aprotic solvent, preferably DMF or DMA, at elevated temperature.

9. A method for preparing a steroidal carbothioate (i.e. the ester of the steroidal carbothioic acid), or a salt thereof, the method comprising;
reacting a steroidal carbothioic acid or a salt thereof, which is prepared as defined in any of the preceding claims, with an electrophilic agent.

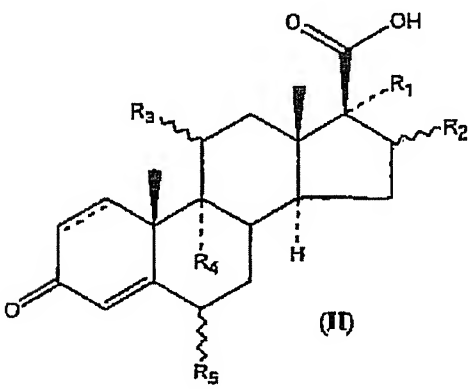
10. A method according to claim 9, in which the electrophilic agent is selected from the group consisting of: C_{1-5} di- or trihaloalkanes, preferably a trihalo- or a dihalomethane, such as chlorobromomethane or bromofluoromethane.

11. A method according to claim 9 or 10 for preparing a steroidal carbothioate of formula (I)



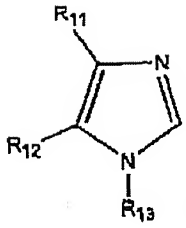
(I)

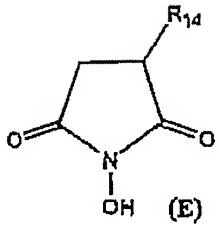
wherein R_1, R_2, R_3, R_4, and R_5 are defined as in claim 7; and
R_{10} represents a C_{1-5} haloalkyl or an optionally substituted heterocyclic ring, the method comprising:
A) reacting a steroidal carboxylic acid of formula (II)



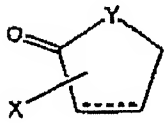
(II)

with a coupling agent and a coupling enhancer [such as a compound of formula (D) or formula (E)]


(D)


(E)

wherein R_{11} and R_{12} independently represent a hydrogen atom or a cyano group (C=N);
R_{13} represent a hydrogen atom or an alkyl group; and
R_{14} represent a hydrogen atom or a moiety of a sulfonic acid, such as sodium sulfonate (eg. the group -S(=O)(=O)-O Na^{+})];
B) reacting the product from step A) with a nucleophilic agent comprising sulfur; and
C) reacting the product from step B) with an electrophilic agent [such as a C_{1-6} di- or trihaloalkane, preferably a trihalo- or a dihalomethane such as chlorofluoromethane or bromofluoromethane] or a compound of the following formula;



wherein X=H, F, Cl, Br and; Y=CH_2, NH, O, S, preferably X=Cl and Y=O.

12. The method of claim 11, wherein the coupling enhancer is selected from the group consisting of: NMI (N-methylimidazole); DCI (4,5-dicyanoimidazole); NHS (N-hydroxysuccinimide); and sulfo-NHS (N-hydroxysulfosuccinimide).

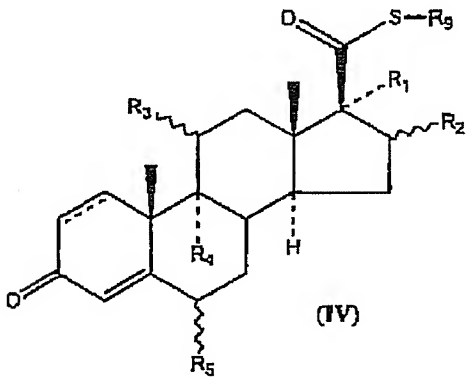
13. The method of any of the claims 11-12, wherein step C) constitutes the *in situ* reaction of the product from step B) with bromofluoromethane to form a compound of formula (I) wherein R_{10} is a fluoromethyl group, such as fluticasone propionate.

14. The method according to any of the preceding claims, in which
- at least two subsequent steps are performed *in situ*, i.e. without any change or removal of solvents, or isolation of the individual intermediates; and/or
- the method is conducted as a continuous method; and/or
- step A), B) and optionally step C) are conducted as a one-pot synthesis without solvent changes and/or are performed at room or elevated temperature.

15. The method of any of the claims 9-14, wherein an androstane 17β-carboxylic acid is converted to an androstane 17β-carbothioate.

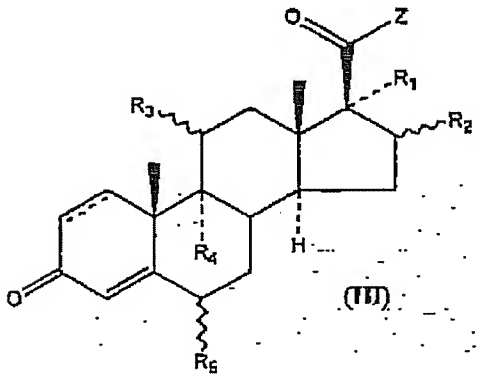
16. The method of any of the preceding claims, wherein step B) provides an alkali metal salt of the thioic acid, such as a compound of formula (IV), in which the moiety -S-R_5 represent a

group of the formula $[-S]^-[M]^+$ wherein M is a metal such as Li, Na or K e.g. $-S^- Na^+$, and the other substituents have the same meaning as defined in claim 7.



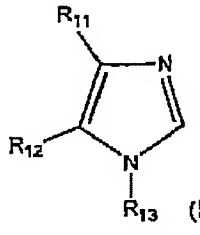
(IV)

17. A compound of the formula (III) and salts and solvates thereof

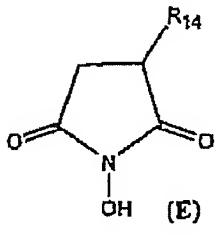


(III)

wherein R_1, R_2, R_3, R_4, and R_5 are defined as in claim 7; and
Z represent the structural moiety resulting from the reaction between the steroidal carboxylic acid of formula (II) and a coupling agent (preferably EDC), followed by a coupling enhancer selected from the group consisting of the compounds of formulas (D); (E); (F); and (G):

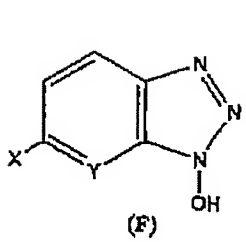


(D)

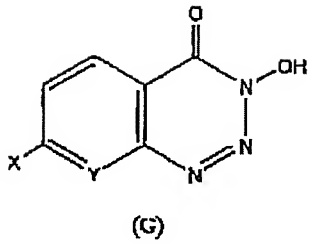


(E)

wherein R_{11} and R_{12} independently represent a hydrogen atom or a cyano group; R_{13} represent a hydrogen atom or a methyl group; and R_{14} represent a hydrogen atom or a moiety of a sulfonic acid, such as sodium sulfonate [ie. the group $-S(=O)(=O)-O^- Na^+$],



(F)



(G)

X - H, F, Cl, Br and Y - CH, N, O, S

with the proviso that:

when the coupling enhancer is a compound of formula (F), X can not represent H when Y represents CH;

When the coupling enhancer is a compound of formula (D), R11 and R12 can not both represent H when R1 in formula III represents OH; and

when the coupling enhancer is a compound of formula (E), R14 can not represent H when R1 in formula III represents H;

and with the further proviso that

succinimidyl-9α-fluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylate;

17α-hydroxy-4-androsten-3-one-17β-carboxylic acid N-hydroxysuccinimide ester;

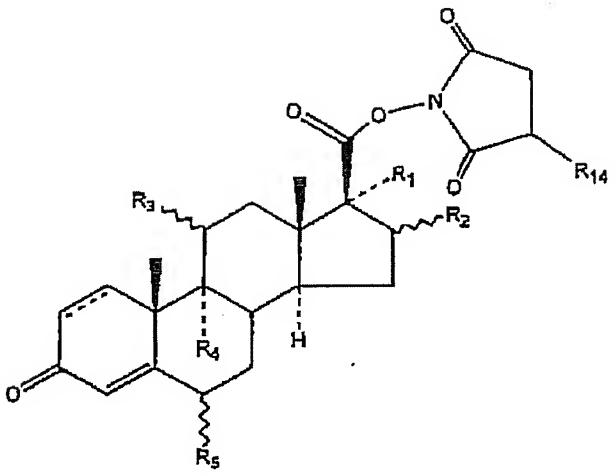
N-hydroxysuccinimidyl-9-fluoro-16α-methyl-11β,17-dihydroxy-3-oxo-1,4-androstadiene-17β-carboxyester;

N-hydroxysuccinimide ester of dexamethasone-17β-carboxylic acid; and

1-[(9α-fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-propionyloxyandrosta-1,4-dien-17β-yl)carbonyl]imidazole are disclaimed.

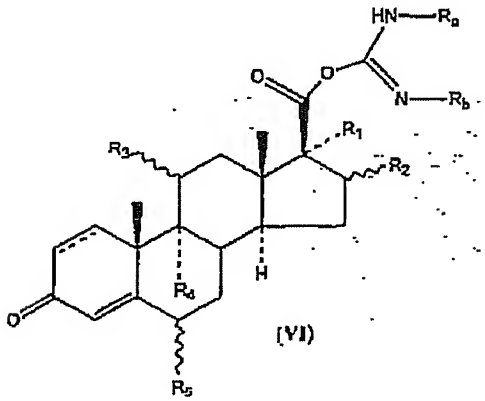
18. The compound of claim 17, wherein at least one of R_{11} and R_{12} is a cyano group (C≡N), and/or R_{13} is a hydrogen atom, and/or formula (D) is NMI (N-methylimidazole) or DCI (4,5-dicyano-imidazole), and/or formula (E) is NHS (N-hydroxysuccinimide) or sulfo-NHS (N-hydroxysulfosuccinimide).

19. The compound having the formula:



in which the substituents have the same meaning as defined in claim 17, and salts and solvates thereof, with the proviso that R14 can not represent H when R1 represents H.

20. A compound of the formula (VI) and salts and solvates thereof



(VI)

wherein R_1, R_2, R_3, R_4, and R_5 are defined as in claim 7; and
R_a and R_b are defined as in claim 1;
with the proviso that 1-(3-dimethylamino-propyl)-3-ethyl-carbodiimide-6α,9α-difluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-3-oxo-androsta-1,4-diene-17β-carboxylate is disclaimed.

21. A composition comprising a compound as defined in any of claims 17-20.

22. Use of a compound of any of the claims 17-20 as an intermediate in a method for preparing a steroidal carbothioate or a steroidal carbothioic acid, such as in a method for preparing fluticasone propionate.

23. Use according to claim 22, in which the method comprises reaction with a nucleophilic agent comprising a sulfur atom and/or comprises reaction with an electrophilic agent.